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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,588	03/09/2006	Taro Yoshikawa	126835	7199

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EXAMINER	
LAU, JONATHAN S	

ART UNIT	PAPER NUMBER
1623	

MAIL DATE	DELIVERY MODE
11/20/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,588	YOSHIKAWA ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 Aug 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,3,4 and 9-14* is/are pending in the application.

4a) Of the above claim(s) *11-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 4, 9 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is responsive to Applicant's Remarks, filed 07 Aug 2008.

This application is the national stage entry of PCT/JP04/11462, filed 10 Aug 2004; and claims benefit of foreign priority document JAPAN 2003-292135, filed 12 Aug 2003; currently an English language translation of this foreign priority document has not been filed.

Claims 1, 3, 4 and 9-14 are pending in the current application. Claims 11-14, drawn to non-elected inventions, are withdrawn.

Election/Restrictions

Applicant's traverse of the election of Group I, claims 1, 3, 4, 9 and 10 as constructively elected by original presentation for prosecution on the merits in the reply filed on 07 Aug 2008 is acknowledged. The traversal is on the ground(s) that the method claims include all the limitations of the product claims and as such are subject to rejoinder upon allowance of the product claims and that a search of any one Group of claims would encompass a search for the subject matter of the remaining claims. This is not found persuasive because the claims are drawn to the product are not presently indicated as allowable, and because a serious search and examination burden is established because the inventions require a different field of search (for example, employing different search queries for the components of a formulation or for methods

of treatment of hepatic diseases or allergy); the prior art applicable to one invention would not likely be applicable to another invention; and/or the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

The requirement is still deemed proper and is therefore made FINAL.

The following rejection is reiterated and maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3 , 4, 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kumagai et al. (US Patent Application Publication US 2002/0115622, published 22 Aug 2002, cited in PTO-892) in view of Koga et al. (Biol. Pharm. Bull., 2003, 26(9), p1299-1305, published online 06 Jun 2003, cited in PTO-892) and Mollica et al. (Journal of Pharmaceutical Sciences, 1978, 67(4), p443-465, cited in PTO-892).

Kumagai et al. discloses a pharmaceutical composition containing 2.0 g glycyrrhizin as the ammonium salt, 20.0 g aminoacetic acid, 1.0 g cysteine hydrochloride (page 3, paragraphs 48-54). In one embodiment this composition is dissolved in 1000 mL water (page 3, paragraphs 46), to give concentrations of 2.0 mg/mL glycyrrhizin as the ammonium salt, 20.0 mg/mL aminoacetic acid, and 1.0 mg/mL cysteine hydrochloride, addressing instant claims 1, 3, 4 and 10. Kumagai et al. discloses formulations may be manufactured using conventional arts (page 3, paragraph 36).

Kumagai et al. does not disclose the specific composition wherein the concentrations are 8 to 16 mg/mL of glycyrrhizin, 3 to 6 mg/mL of cysteine and 80 to 160 mg/mL of aminoacetic acid (instant claim 1). Kumagai et al. does not disclose a composition wherein the concentrations are 8 to 16 mg/mL of monoammonium glycyrrhizinate, 4 to 8 mg/mL of cysteine hydrochloride and 80 to 160 mg/mL of aminoacetic acid (instant claim 10). As convincingly argued, Kumagai et al. does not disclose a composition wherein substantially no sulfite is contained (instant claims 1, 3, 4, 9 and 10).

Koga et al. teaches a highly concentrated glyccyrhizin solution that is stable against precipitation as a gel (page 1299, right column, lines 3-10). Koga et al. teaches that a highly concentrated glyccyrhizin preparation is desirable because glyccyrhizin was detectable in plasma following oral administration of a large dose (page 1299, left column, lines 12-15). Koga et al. provides evidence that it is an expected result that an increased concentration of glycyrrhizin remains soluble, or stable, when in the presence of increased concentration of buffer (page 1301, right column, lines 4-10).

Mollica et al. teaches undesired "extrachemical" reactions can occur when stabilizing excipients are added to drug formulations (page 448, right column, lines 31-35). Mollica et al. teaches sodium bisulfite can cause precipitation of the drug from the formulation (page 449, left column, lines 2-3).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the pharmaceutical composition containing ammonium glycyrrhizinate of Kumagai et al. with the increased concentration taught by Koga et al. and the omission of sodium bisulfite taught by Mollica et al. Koga et al. teaches that a highly concentrated glyccyrhizin preparation is desirable because glyccyrhizin was detectable in plasma following oral administration of a large dose (page 1299, left column, lines 12-15) and provides evidence that it is an expected result that an increased concentration of glycyrrhizin remains soluble, or stable, when in the presence of increased concentration of buffer (page 1301, right column, lines 4-10). "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such

concentration or temperature is critical." See MPEP 2144.05(II). As it is an expected result that an increased concentration of glycyrrhizin remains stable in the presence of increased concentration of buffer, no evidence is provided indicating the instantly claimed concentration range is critical. The function of sodium bisulfite is "stabilization due to sodium bisulfite", not stabilization in all aspects. The elimination of sodium bisulfite and the function of "stabilization due to sodium bisulfite" is obvious. See MPEP 2144.04(II)A. The function of "stabilization due to sodium bisulfite" is not desired because Koga et al. discloses the function of stabilization of an increased concentration of glycyrrhizin due to increased concentration of buffer. One would be motivated to eliminate sodium bisulfite because Mollica et al. teaches undesired "extrachemical" reactions can occur when stabilizing excipients are added to drug formulations (page 448, right column, lines 31-35), for example Mollica et al. teaches sodium bisulfite can cause precipitation of the drug from the formulation (page 449, left column, lines 2-3).

Instant claim 9 recites a property that is presumed to be inherent to the composition. As evidenced by the Merck Index (The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals, 2006, Merck & Co., Inc., Whitehouse Station, NJ, USA, 14th Edition, cited in PTO-892), cysteine is freely soluble in water, alcohol, acetic acid, and ammonia water. Therefore, Kumagai et al. in view of Koga et al. and Mollica et al., in rendering instant claim 1 unpatentable as recited above also renders instant claim 9 unpatentable.

Response to Applicant's Remarks:

Applicant's Remarks, filed 07 Aug 2008, have been fully considered and found not to be persuasive.

Applicant remarks, regarding the overlap of ranges discussed in MPEP 2144.05 I, that the claimed ranges are not close enough that one skilled in the art would have expected them to have the same properties and therefore a *prima facie* case of obviousness is not shown. However, the rejection reiterated above does not rely on the prior art ranges being close enough that one skilled in the art would have expected them to have the same properties. MPEP 2144.05 II.A., quoted in the rejection reiterated above, provides guidance that a *prima facie* case of obviousness is also established in cases where differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. In the instant case, a *prima facie* case of obviousness is shown because "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2144.05 II.A. Remarks regarding whether the prior art ranges are close enough that one skilled in the art would have expected them to have the same properties do not rebut the case that optimization of ranges by routine experimentation in the absence of evidence indicating such concentration or temperature is critical is *prima facie* obvious.

Applicant notes that Koga teaches increased phosphate buffer concentration improved GZ [glycyrrhizin] solubility. Applicant asserts that the teaching of Koga is

drawn to specifically the effect of phosphate on glycyrrhizin solubility. However, Koga teaches glycyrrhizin solubility is dependent on pH (page 1301, left column, paragraph 3), rather than specifically the effect of the phosphate in the buffer. Koga teaches it is adjustment of the pH, not the presence of phosphate, which increases solubility (page 1304, left column, paragraph 1). Therefore one of ordinary skill in the art would have a reasonable expectation of success in applying the teaching of Koga using other buffers to adjust the pH in order to improve glycyrrhizin solubility.

Applicant remarks that it is asserted that cysteine hydrochloride and aminoacetic acid alone should act as a sufficient stabilizer for glycyrrhizin in the presence of sodium sulfite based on Examiner's reading of the teachings of Koga et al. However, the rejection is based on Kumagai et al. in view of Koga et al. and Mollica et al. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant remarks that Mollica does not teach the specific effect of sodium sulfite on glycyrrhizin, teaching only sodium sulfite to cause precipitation of imipramine hydrochloride. However, Mollica teaches it is known in the art that Mollica et al. teaches sodium bisulfite can cause precipitation of the drug from the formulation (page 449, left column, lines 2-3). Mollica teaches it is within the level of ordinary skill in the art to optimize the drug formulation for drug product stability (page 443, right column, paragraphs 2-4), applying the teaching of the effect of sodium sulfite to cause precipitation of imipramine hydrochloride to other drugs in drug formulations.

This rejection is maintained and made FINAL.

Conclusion

No claim is found to be allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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